Renal Cell Carcinoma

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Renal Cell Carcinoma

- Originate within the renal cortex and are responsible for 80-85 % of all primary renal neoplasms
- Next most common primary renal neoplasm is transitional cell carcinoma accounting for 8%
- Infrequent primary tumors include: oncocytomas, collecting duct tumors, and renal sarcomas
- Nephroblastoma or Wilms’ tumor is common in children

Epidemiology

- In 1998, renal cell carcinoma was diagnosed in 30,000 individuals in the U.S., representing 2-3% of all cancers
- The incidence of RCCA has increased over time: in the U.S., between 1975-1995, incidence rates have increased for white men by 2.3%, white women by 3.1%, black men by 3.9%, and black women by 4.3% (WH Chow et al, JAMA 1999)
- Highest rates observed in Scandinavia and North America
- Whites and blacks equally affected in the U.S.

Epidemiology

- RCCA frequency thought to be 2:1 (male:female), but recent data suggests that the gap is narrowing
- RCCA occurs usually in sixth to eighth decade of life, being unusual in patients < 40 years old
- Number of deaths from RCCA has been decreasing mostly due to early diagnosis
- 5 year survival rate for those diagnosed in 1974-1976 was 52%, whereas for those diagnosed in 1986-1993 the 5 year survival was 60%

Risk Factors

- Cigarette smoking increases the probability of developing RCCA twofold
- Occupational exposure to toxic compounds such as cadmium, asbestos, and petroleum by-products
- Obesity; there is a direct correlation between increased body weight and enhanced risk of developing RCCA (MC Yu et al, J Natl Cancer Inst 1986)

Risk Factors

- 35-50% of chronic dialysis patients develop acquired cystic disease, and 6% of whom develop RCCA (LD Truong et al, Am J Kidney Dis 1995)
- Malignancy generally develops after 8-10 years of dialysis
- Males along with patients with cysts that result in an increase in kidney size are at increased risk for malignant transformation
- RCCA does not occur with increased frequency in polycystic kidney disease when compared to general population

Genetic Factors

- Enhanced risk of RCCA observed in patients with inherited disorders such as von Hippel-Lindau disease and tuberous sclerosis
- Von Hippel-Lindau: autosomal dominant, abnormalities in chromosome 3p, predisposition to variety of neoplasms, RCCA develops in 1/3 of patients
- Tuberous sclerosis: autosomal dominant, affects genetic loci on chromosome 9 and on chromosome 16p, characterized by formation of angiomyolipomas in the skin, brain, kidneys, and other organs. RCCA occurs in < 5% of patients

Renal Cell Carcinoma

- Additional clinical factors which may be associated with development of RCCA include:
- Hypertension
- Unopposed estrogen therapy
- Prior radiation therapy

Pathology

- Renal cell tumor diameter ranges from less than 2 cm to greater than 25 cm
- Lesions smaller than 3 cm were previously thought to represent benign adenomas, but now it is known that even small tumors can represent RCCA (MA Bosniak et al, Radiology, 1995)
- As a result, histologic criteria is needed to determine malignant vs benign growth, and all solid renal masses require resection for diagnosis, unless a metastatic lesion can be biopsied

Pathology

- 5 distinct subtypes have been identified:
- Clear cell (75-85% of tumors)
- Chromophilic (15% of tumors)
- Chromophobic (5% of tumors)
- Oncocytic (uncommon)
- Collecting duct (very rare)

Pathology

- Clear cell carcinoma: arises from proximal tubule cells, has deletion at chromosome 3p, has poor prognosis with presence of a sarcomatoid pattern
- Chromophilic carcinoma: also known as papillary carcinoma, also arises from proximal tubule cells, associated with multiple genetic abnormalities but no abnormality in 3p, frequently multifocal and bilateral, commonly presents as a small early stage tumor and therefore usually has a favorable prognosis

Pathology

- Chromophobic carcinoma: originates from cortical collecting duct and is composed of sheets of cells which are darker than cells of clear cell carcinoma because they lack lipid and glycogen, exhibits wide variety of genetic abnormalities but shows no deletion at chromosome 3p, has excellent prognosis
- Oncocytoma: consists of large well differentiated neoplastic cells with a large number of mitochondria, originates from collecting duct cells, usually behaves in a benign fashion with rare local invasion and rare metastases
- Collecting duct tumor: rare but usually very aggressive

Pathogenesis

- Clear cell carcinomas often reveal chromosomal losses in 3p14 to 3p26, and in von Hippel-Lindau there are chromosomal abnormalities in a similar area, 3p25 to 3p26; so common genetic abnormality may be involved in both disorders
- VHL protein is expressed at high levels in the kidney suggesting that it is required for normal function; role of VHL protein includes suppression of transforming growth factor-beta 1 and it decreases stability of transforming growth factor-alpha mRNA

Pathogenesis

- Analysis of sporadic clear cell carcinomas have showed that a large number of tumors have VHL mutations (Out of 110 patients with sporadic clear cell carcinomas, VHL mutations were found in 57% of tumors; JR Gnarra et al, Nat Genet 1994)
- So, this suggests that the VHL gene is a tumor suppressor gene which when inactivated contributes to the development of malignancy

Pathogenesis

- Development of RCCA may also involve abnormalities in genes which control cell division, which includes p53 tumor suppressor gene
- Expression of p53 may be associated with more aggressive behavior (In one series of 175 patients, 10 year survival was lower in the tumors staining for p53, 48% vs 78% 10 year survival; DL Uhlman et al, J Natl Cancer Inst 1994)
- p53 also implicated in IL-6 overexpression which may cause reduced responsiveness to immunotherapy and the clinical manifestations seen in advanced RCCA (JY Blay et al, Cancer Res 1992)

Clinical Features

Presentation:

- Patients with RCCA present with a wide array of symptoms and/or laboratory abnormalities and therefore it has been labeled the “internist’s tumor”
- Many patients are asymptomatic until the disease is advanced, and at presentation 25% of patients have distant metastases or significant local disease
- Classic triad of RCCA is flank pain, hematuria, and palpable abdominal mass which is uncommon, but when present suggests advanced disease

Clinical Features

Signs and Symptoms:

- Hematuria; observed only with tumor invasion of collecting system, and when severe may cause clots and resultant “colicky” pain
- Abdominal mass; associated with lower pole tumors and is usually firm, homogeneous, nontender, and moves with respiration
- Scrotal varicocele; majority are left sided and usually fail to empty when the patient is recumbent because the tumor has obstructed the gonadal vein where it enters the renal vein

Systemic Symptoms

- Common sites of metastases include lung, lymph nodes, bone, liver, brain, ipsilateral adrenal gland, and the contralateral kidney
- So, patients may present with pathologic fractures, cough, hemoptysis, dyspnea, or enlarged lymph nodes
- With vena caval involvement, one can have ascites, hepatic dysfunction related to Budd-Chiari syndrome, and pulmonary emboli

Systemic Symptoms

- Fever; occurs in 20% of patients and is usually accompanied by night sweats, anorexia, weight loss, and fatigue
- Amyloidosis; secondary amyloidosis is found in 3-5% of patients and this occurs because the amyloid A protein is an acute phase reactant (M Pras et al, Am J Med 1982)
- Anemia of chronic disease
- Hepatic dysfunction can occur without metastatic disease to the liver, which may result from tumor production of cytokines such as GM-CSF and IL-6 (JY Blay et al, Int J Cancer 1997)

Systemic Symptoms

- RCCA may produce a host of hormones which may be associated with paraneoplastic phenomena:
- Erythropoietin
- Parathyroid hormone -related protein
- Gonadotropins
- Renin
- Glucagon
- Insulin
- Human chorionic somatomammotropin

Systemic Symptoms

- Erythrocytosis; occurs in 1-5 % of patients with RCCA usually due to production of erythropoietin. Also, it may be secondary to mutated VHL protein and resultant impaired regulation of hypoxia-induced proteins (AP Levy et al, Kidney Int 1997)
- Hypercalcemia; occurs in 15% of patients with RCCA due to lytic bone metastases and overproduction of PTHrP, it carries a poor prognosis
- Long-acting bisphosphonates are the treatment of choice for hypercalcemia and such therapy has added benefit of reduction in bone mets.

Systemic Symptoms

- Bone resorption by the tumor results in release of growth factors that promote further tumor growth
- So, by inhibiting bone resorption with a bisphosphonate, the environment that promotes tumor growth is altered (GR Mundy et al, N Engl J Med 1998)

Radiologic Evaluation

- Patient with signs and symptoms of RCCA must undergo radiologic evaluation
- Ultrasound is able to distinguish a simple benign cyst from a more complex cyst or a solid tumor
- There are three criteria on US that indicate a simple cyst: mass is round and sharply demarcated with smooth walls, there are no echoes within the mass, there is a strong posterior wall echo indicating good transmission through the cyst
- In one study, the accuracy of US in evaluating renal masses was assessed retrospectively in 260 lesions; 168 were benign cysts and 92 were RCCA, all diagnosed correctly by US (RV Clayman et al, Am J Med 1984)

Radiologic Evaluation

- If criteria for a simple cyst by US not satisfied, then patient should undergo CT scan
- On CT, criteria for a simple cyst include: smooth appearance, no enhancement with IV contrast, and is density of water
- MRI is useful when US and CT are nondiagnostic and/or IV contrast is contraindicated

Staging

- Local involvement of RCCA is principally determined by CT scan of the abdomen, which is extremely accurate in staging RCCA
- In one retrospective study of 100 RCCAs, preoperative CT scans were compared with findings obtained at surgery. Overall, CT scanning correctly assessed 91% of patients with regards to vein invasion, metastatic adenopathy, and local invasion (CD Johnson et al, AJR 1987)
- Staging should also include CT of chest and a bone scan

Modified Robson and TNM Staging Systems

- Stage I: confined by renal capsule; T1(small), T2(large), N0, M0
- Stage II: through renal capsule; T3A, N0, M0
- Stage IIIa: renal vein involvement; T3B, N0, M0
- Stage IIIb: lymphatic involvement; T1-3B, N1-4, MO
- Stage IV: metastatic spread; T1-3B, N0-4, M1

(MB Garnick et al, Genitourinary Oncology 1996)

Prognosis

- Patients with disease confined locally have a good prognosis. For example, patients with T1 and T2 lesions have five-year survival rates of >90% (C Selli et al, Cancer 1983)
- Patients with invasive disease involving lymph nodes and/or metastatic involvement have a poor long term prognosis. For example, patients with Robson stage IIIb have a 2 year disease free survival rate of <25% (J Fleischmann et al, 1997)

Prognosis

- Clinical factors may also affect survival, such as anemia, hypercalcemia, hepatopathy, fever, and weight loss.
- In one study, among patients with stage IV disease, the median survival of patients with hypercalcemia was lower than in eucalcemic patients, 45 days vs 286 days (HJ Fahn et al, J Urol 1991)

Screening

- The following patients at high risk for the development of RCCA should undergo periodic radiologic monitoring with US or CT:
- Patients with von Hippel-Lindau or tuberous sclerosis
- Patients with ESRD on dialysis for 3-5 years
- Patients with strong family history of renal cancer
- Patients with history of prior kidney irradiation

Surgical Management based upon Staging

- Stages I and II: surgery may be curative and patients should undergo either a radical or partial nephrectomy. Criteria for partial nephrectomy include bilateral tumors, solitary kidney, compromised renal function, tumor <4cm, and polar tumors
- Stage III: patients with tumor invading the adrenal gland or surrounding tissue should undergo a radical nephrectomy. Patients with abdominal lymph node involvement are also candidates for radical nephrectomy, because these nodes may only have reactive inflammation

Radical Nephrectomy

- Radical nephrectomy consists of early ligation of the renal artery and vein, and excision of the kidney, Gerota's fascia, and ipsilateral adrenal gland
- This became procedure of choice in the 1960s when a study reported a five year survival rate of 66% compared to 48% with simple nephrectomy (CJ Robson, J Urol 1963)
- Most Urologists will extend a partial nephrectomy to a radical procedure when sarcomatoid histology is found on frozen section or with evidence of renal vein invasion

Partial Nephrectomy

- Concern with partial nephrectomy is that a multicentric tumor would be missed and result in recurrent disease
- Recurrent disease is less likely if this procedure is selected for patients with early stage disease and small tumor size. For example, one study looked at 70 patients with T1 or T2 disease and average tumor size of 3 cm who underwent partial nephrectomy. At 10 year follow up, no recurrence was found in 69 patients (HW Herr, J Urol 1999)

Surgical Management of multiple and/or bilateral tumors

- In von Hippel-Lindau disease we often see multiple and/or bilateral tumors
- In this case, renal-sparing enucleation of tumors is performed rather than nephrectomy to preserve renal function
- Continued monitoring is required after enucleation, since recurrence occurs in VHL; 30% of patients at five years and 85% at ten years (D Chauveau et al, Kidney Int 1996)
- Laparoscopic cryotherapy or radiofrequency ablation are being tried for multiple or bilateral tumors in attempt to minimize damage to normal kidney

Inferior vena caval involvement

- Commonly associated with metastases and right sided tumors, and occurring in 5% of patients undergoing radical nephrectomy, is inferior vena caval involvement with tumor thrombus
- Operative mortality is high reaching 5-10% and five year survival is dismal

Resection of Metastatic Disease

- In combination with nephrectomy, it is not uncommon to resect solitary or oligometastases, which are often in the ipsilateral lung or adrenal gland
- In one study of 278 patients, 51% underwent removal of metastases, 25% underwent just nephrectomy, and 24% did not have surgery. The five year survival for those undergoing metastatectomy was 44%, and the survival for the other two groups was 14% and 11% respectively (JP Kavolius et al, J Clin Oncol 1998)
- Also, resection of metastatic disease is effective following systemic therapy with IL-2

Radiation Therapy

- Radiation therapy used as an adjuvant to nephrectomy is currently considered unproven since no well-designed trial has been performed
- However, radiation treatment of the major sites of metastases may provide pain relief and ameliorate consequences such as cord compression or airway obstruction
- Stereotactic radiation may be effective for patients with <3cm CNS metastases. In one series, 90% were free from local failure at one year and only 1/3 developed new mets. (GV Dave et al, Cancer Ther 1998)

Medical Management

- Medical treatment of RCCA is considered in patients who are not candidates for curative surgery (significant local disease or distant multiple metastases) and for patients with disease that has recurred after surgery
- Hormonal therapy and chemotherapy have shown no benefit in the treatment of RCCA
- So, the major focus over the past decade has been immunotherapy

Immunotherapy

- RCCA evokes an immune response which occasionally results in spontaneous remission
- In an attempt to reproduce this response, various strategies have been used to include:
- Nonspecific stimulators of the immune system
- Specific antitumor immunotherapy
- Adoptive immunotherapy
- Administration of partially purified or recombinant cytokines

Interferon alfa

- Effectiveness of IFNa in metastatic RCCA has been evaluated
- One recent trial randomized 350 patients to subcutaneous IFNa or oral medroxyprogesterone. IFNa resulted in improved one year survival , 43% vs 31%. (Renal Cancer Collaborators, Lancet 1999)
- Overall, 15% of patients given IFNa respond, but the response is delayed, partial, and short-lived. Only 2% of patients have complete responses
- No clear dose exists, but daily doses ranging from 5-10 MU have highest therapeutic index
- There has been promising results for combination therapy with cis-retinoic acid, leading to phase III trial

Combination therapy

- Single agent Interferon gamma therapy has minimal or no activity in patients with RCCA
- Combination therapy of IFNa plus IFNg has shown some promising results. In one trial, coadministration produced responses in 8 of 30 patients and 2 patients had complete responses (MS Ernstoff et al, J Clin Oncol 1990)

Interleukin-2

- In 1995, the FDA approved high dose bolus IL-2 for the treatment of metastatic RCCA based upon data from study involving 255 patients. IL-2 (600,000-720,000 IU/kg) was administered by 15 minute infusions every 8 hours for 14 consecutive doses. Treatment was repeated at 12 week intervals in responders for three cycles. (G Fyfe et al, J Clin Oncol, 1995)
- Although response rate was only 14% and there was a high level of toxicity involved, the individual responses were impressive. 60% of responders had >90% regression of disease

Interleukin-2

- In attempt to limit systemic toxicity but retain potent antitumor activity, different routes have been evaluated including continuous intravenous infusion, inhalation therapy, outpatient subcutaneous therapy, and low dose intravenous therapy
- Continuous IV infusion: studies show that there is no difference in incidence of life-threatening toxic side effects between randomized groups (GR Weiss et al, J Clin Oncol, 1992)
- Inhalation therapy: Although safe, uncertain whether it provides any benefit

Interleukin-2

- Outpatient subcutaneous administration: in one study of 27 patients, daily dosing resulted in 22% response rate (DT Sleijfer et al, J Clin Oncol 1992)
- Low dose intravenous therapy: produces significantly less hypotension, thrombocytopenia, malaise, pulmonary toxicity, and neurotoxicity than high dose therapy. However, response rates were 19% for high dose and 10% for low dose and responses to high dose were more durable (JC Yang et al, Cancer J Sci Am, 1997)

Interleukin-2

- IL-2 is a strong stimulator of proinflammatory cytokines (IL-1, TNFa, and IFNg) and these substances may cause a substantial portion of the toxicity related to therapy. In comparison, the antitumor effect of IL-2 is mediated by cellular imune mechanisms
- So, the toxicity of IL-2 may be dissociated from its antitumor effects by administering cytokine inhibitors
- IFNa upregulates the expression of tumor associated antigens, thereby possibly increasing susceptibility of tumor cells to IL-2 mediated lysis. So, trials of combination therapy are currently under investigation.

Immunotherapy

- Other immunotherapeutic agents which are currently being evaluated include IL-4, IL-6, IL-12 (alone and in combination with IL-2), and Flt3 ligand
- Antiangiogenesis therapy may be promising for RCCA, since in the majority of clear cell RCCA there is the mutated VHL gene, and this gene regulates vascular endothelial growth factor production. Initial studies show antitumor activity with antibodies directed against VEGF (MS Gordon et al, Proc ASCO 1998)
- Response to immunotherapy is most frequent with clear cell type, but there is a paucity of data regarding effectiveness in other types